REMARKS

Claims 1-72 are pending in the present application. Claims 5, 6, 8, 9, 11, 14, 15 and 17-72 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-4, 7, 10, 12, 13, and 16 are currently under examination.

Amendments to Claims

Claims 7 and 10 have been amended herein to correct a clerical error related to the amino acid residue number. Support for the amendment can be found in the claims themselves, and in particular, in the as-filed claims. For example, as-filed claim 7 includes multiple references to amino acid mutations from one amino acid to another at a given position in the polypeptide sequence, in reference to the polypeptide sequence of SEQ ID NO:5. These references to amino acid mutations, when the references are considered collectively, evidence a clerical error in the numbering of the amino acid residues of SEQ ID NO:5 as set forth in the claims.

Specifically with regards to claims 7 and 10, the as-filed claims defined the mutation as a "substitution from threonine to alanine at amino acid residue number 393 . . . relative to the amino acid sequence . . . SEQ ID NO:5." However, in SEQ ID NO:5 as filed, the amino acid residue number of the threonine residue is at amino acid residue number 391, rather than at 393. Therefore, the claims are amended herein to properly reflect the numbering of SEQ ID NO:5.

Also at this time, claims 2, 4, 7, 10, 12, 13 and 16 have been amended to address the changes required as a result of Applicants' election in response to the restriction requirement.

Restriction Requirement

Applicants acknowledge that the Examiner has deemed the mutation restriction proper and has made the mutation restriction final. In electing the mutation at amino acid position 393 (which has herein been amended to recite "position 391" as set forth in detail above), and amending the pending claims in accordance with the election, Applicants make no assertion as to the relatedness of the sequences or claims restricted by the Examiner, but instead, merely respond to the Examiner's restriction.

Priority

The Examiner alleges that claims 4-16 contain limitations, such as SEQ ID NO:5 and SEQ ID NO:11, that are not disclosed in the provisional application 60/443,364 and thus cannot claim priority to the provisional application, and therefore instead have a priority date of January 29, 2004.

Applicants respectfully submit that all claims referring to SEQ ID NO: 5 (such as 4, 7, 10, and 13) should properly be granted priority of the provisional application 60/443,364 because, although a separate sequence listing was not submitted with the provisional application, the sequence depicted in SEQ ID NO: 5 was nonetheless disclosed in provisional application 60/443,364.

Specifically, SEQ ID NO: 5 is the amino acid sequence of HIV-2/VCP gp120. The sequence modifications disclosed and described in the provisional application were described with reference to the HIV-2/VCP gp120 (see, for example, provisional application 60/443,364, page 3, line 7). The sequence modification termed ΔV3(6,6), in both the provisional application and the present application as filed, is described in the provisional application on page 9, beginning on line 30, as a "deletion of the V3 loop (leaving only the first 6 and last 6 amino acids)." The HIV-2/VCP gp120 sequence was previously disclosed in Lin et al. (J. Virology, Nov. 2001, vol. 75, no. 22, pp 10766-10778; see, in particular, Figure 6; note also that this reference is cited generally in the provisional application on page 9, line 25) by virtue of its comparison to a previously disclosed and described gp120 sequence known as HIV-2/NIHz (see Zagury et al., PNAS, Aug. 1988, vol. 85, pp. 5941-5945; see, in particular, Figure 1). Therefore, although SEQ ID NO:5 itself was not submitted in a sequence listing with the provisional application, the genetic modifications described in the provisional application were described with reference to a previously disclosed HIV-2/VCP gp 120 sequence, the identical sequence depicted in SEQ ID NO:5. For the foregoing reasons, Applicants respectfully request that claims 4, 7, 10, and 13 be given priority to the provisional application 60/443,364.

Applicants note that the specific sequence set forth in SEQ ID NO:11 is not disclosed in the provisional application 60/443,364 and therefore, claims having this limitation, i.e., claims 12 and 16, are entitled to a priority date of January 29, 2004, the filing date of the present application.

Rejection of claims 1-5, 7, 10, 12, 13, and 16 under 35 U.S.C. § 112, second paragraph

Claims 1-5, 7, 10, 12, 13, and 16, stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

First, the Examiner is of the opinion that the "metes and bounds" of the term mutant are not clear and that although the specification as filed, in the Examiner's words, "defines mutants as peptides, which may be altered in one or more amino acids," the Examiner contends that the specification as filed "does not define the type of alteration to be made in order to obtain a mutant" polypeptide. Applicants respectfully submit that the specification as filed does in fact define the type of alteration to be made in order to obtain a mutant polypeptide on page 27, beginning line 24, which states: "A "mutant" polypeptide as used in the present application is one which has the identity of at least one amino acid altered when compared with the amino acid sequence of the naturally-occurring protein. Further, a mutant polypeptide may have at least one amino acid residue added or deleted to the amino acid sequence of the naturally-occurring protein."

Second, the Examiner is of the opinion that the term "derivative" is not one that has a universally accepted meaning in the art, that it has not been adequately defined in the specification, and that in the absence of a single recognized meaning for the term, one of skill in the art could not determine the metes and bounds of the claims. Applicants submit that, consistent with its use in the application as filed, and consistent with how one skilled in the art would understand it, the term "derivative" means "a compound . . . obtained from another compound by a simple chemical process." (Derivative. Def. 1. *Grant & Hackh's Chemical Dictionary*, 5th ed, McGraw-Hill Book Company, New York, 1987). Consistent with this definition, in the specification as filed, on page 45, beginning on line 3, Applicants defined the term "derivatives" as "peptides which may be altered in one or more amino acids (or in one or more base pairs) such that the peptide (or DNA) is not identical to the sequences recited herein, but has the same property as the peptides disclosed herein, in that the peptide has the property of having a detectable function compared with the wild type polypeptide." Therefore, consistent with its usage in the application as filed, a "derivative" would include any gp120 polypeptide which in its entirety, or in part, has a substantially similar amino acid sequence to gp120, and which retains at least one property of gp120. Derivatives of gp120 may be characterized by

single or multiple amino acid substitutions, deletions, additions, or replacements and would include derivatives in which one or more amino acid residues of gp120 are substituted with conservative or non-conservative amino acids, derivatives in which one or more amino acids are added to gp120, derivatives in which one or more of the amino acids of gp120 includes a substituent group, derivatives in which gp120 or a portion thereof is fused to another peptide, derivatives in which one or more nonstandard amino acid residues (i.e., those other than the 20 standard L-amino acids commonly found in naturally occurring proteins) are incorporated or substituted into the gp120 sequence, and derivatives in which one or more non-amino acid linking groups are incorporated into or replace a portion of gp120.

For the reasons stated above, Applicants respectfully submit that the rejection of claims 1-5, 7, 10, 12, 13, and 16 has been overcome and request reconsideration and withdrawal of the present rejection.

Rejection of claims 1-5, 7, 10, 12, 13, and 16 under 35 U.S.C. § 112, first paragraph

Claims 1-5, 7, 10, 12, 13, and 16, stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. The Examiner contends that claims 1-5, 7, 10, 12, 13, and 16, contain subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner contends that the claims are drawn to an isolated nucleic acid encoding a mammalian immunodeficiency virus glycoprotein gp120 polypeptide or fragment thereof, but that the specification provides insufficient distinguishing identifying characteristics of the genus. Applicants respectfully disagree for the following reasons, and submit that the claimed invention is supported by an ample written description.

Applicants remind the Examiner that the MPEP sets the standard for the Examiner's burden in making a rejection based on an alleged lack of written description:

> A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of **presenting by a preponderance of evidence** why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d at 263, 191 USPQ at 97. (emphasis added).

Applicants respectfully submit that the Examiner has not met this burden.

Applicants contend that they have indeed provided sufficient written description as required by the applicable law. In the landmark case of *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit traced the development of the written description requirement under 35 U.S.C. §112, first paragraph. The *Vas-Cath* Court, in a unanimous opinion, noted approvingly that in a written description analysis, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath*, 19 USPQ2d at 1116 (quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)) (emphasis added). After discussing the policy reasons underlying the requirement, the Court set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use;" the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

In the present application, Applicants have provided abundant guidance to the skilled artisan, with respect to the written description of the invention. For example, the specification as filed provides that the term "fragment," as applied to a polypeptide, "may ordinarily be at least about seven contiguous amino acids, typically, at least about fifteen contiguous amino acids, more typically, at least about thirty contiguous amino acids, typically at least about forty contiguous amino acids, preferably at least about fifty amino acids, even more preferably at least about sixty amino acids and most preferably, the peptide fragment will be greater than about sixty contiguous amino acids in length." Page 44, line 6. Additionally, throughout the Experimental Examples in the specification, Applicants set forth multiple specific examples of gp120 polypeptides according to the present invention.

Furthermore, Applicants define "fragment" with particularity as it relates to the claimed invention, at lines 5-17 on page 42 of the specification. Specifically, Applicants define

fragments of the invention by the activity of the fragment: "Further, biological activity, as it refers to any form or fragment of Env, means that the polypeptide has the ability to bind to a chemokine receptor protein without the requirement that it also bind to CD4. Given the evidence that viral entry involves a series of sequential and coordinated conformational changes in gp120 and gp41, and the view that these changes will involve the creation of new epitopes that will be better exposed in variable loop deleted viruses, biological activity also refers to any polypeptide that has the ability to block viral entry or virus Env-mediated fusion."

The skilled artisan would have no question as to the specific properties and characteristics of a "fragment" of a polypeptide according to the present invention. For example, the skilled artisan would understand that, in one embodiment, a "fragment" according to the claimed invention would necessarily share amino acid sequence homology with SEQ ID NO:5, and further, that such a fragment would possess some degree of biological activity as described in the specification. Therefore, the pending claims do comply with the written description requirement of the USPTO, because the specification provides sufficient identifying characteristics of the claimed polypeptides. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description rejection of claims 1-5, 7, 10, 12, 13, and 16.

Rejection of claim 1 under 35 U.S.C. § 102(b)

The Examiner has rejected claim 1 under 35 U.S.C. § 102(b) as being anticipated by Hasel et al. (1999, US Pat No 5,886,163; "Hasel"). Specifically, the Examiner contends that Hasel discloses a recombinant nucleic acid molecule, which encodes a mutant HIV-1 gp120 envelope glycoprotein comprising a V3 loop deletion and a C4 domain point mutation and thus anticipates claim 1 of the current application.

Applicants respectfully submit that Hasel does not anticipate the present invention for the following reasons. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)

(emphasis added). Therefore, Hasel must describe each and every element of claim 1 in order to anticipate this claim under 35 U.S.C. §102(b). This reference does not satisfy this requirement.

Hasel recites, in claim 1: "[a] recombinant nucleic acid molecule which encodes a mutant HIV-1 gp120 envelope glycoprotein comprising a V3 loop deletion and a C4 domains $_{(w->x)}$ point mutation, wherein X is an amino acid residue other than tryptophan." According to Hasel, the C4 domain $_{(w->x)}$ point mutation is a mutation of the conserved tryptophan residue after residue X_{10} to an amino acid other than tryptophan (Hasel et al., 1999, US Pat No 5,886,163, beginning page 9, line 4), based upon existing C4 domain sequence information from various HIV-1 strains and which has a conserved tryptophan residue after residue X_{10}. (Hasel et al., 1999, US Pat No 5,886,163, beginning page 8, line 49). In other words, Hasel claims a nucleic acid molecule which encodes a mutant HIV-1 gp120 envelope comprising a V3 loop deletion and an amino acid substitution at a specific position within the C4 domain. The stated purpose for the specific amino acid substitution of Hasel is: "[t]he point mutations . . . are selected based on their ability to reduce the affinity of the mutant gp120 glycoprotein . . . for CD4 . . . by at least two-fold." (see page 10, line 32). Examples of specific amino acid substitutions are indicated in the Hasel Figure 1 caption, which explains that point mutations in the C4 domain "reduce gp120 binding to cell surface CD4." (page 5, line 63).

In contrast, in the current application as filed, beginning on page 36, line 19, the term "compensatory mutation" is defined as referring to:

> [O]ne or more specific amino acids in a polypeptide sequence, where the identity of the amino acid(s) differs from that found at the same position(s) in the wild type polypeptide sequence, <u>for the purpose or with the result of altering the properties and/or activity of the polypeptide in response to a second change affecting the properties and/or activity of the polypeptide</u>. For example, in response to the deletion of a stabilizing domain from a polypeptide sequence, one or more amino acid mutations may be induced in the remaining polypeptide sequence in order to detectably increase the stability of the truncated polypeptide compared with the stability of the polypeptide under otherwise identical conditions but in the absence of the mutation. <u>As disclosed herein, deletion of a hypervariable region can mediate a detectable loss or decrease in a virus function or activity. A compensatory mutation is any mutation in another region of the polypeptide, or in another polypeptide, that detectably increases the level of the function or activity affected by the deletion</u>. (emphasis added)

As described above, in Hasel, the purpose for the point mutation at a specific position in the C4 domain is to "reduce gp120 binding to cell surface CD4" and to "reduce the

affinity of the mutant gp120 glycoprotein encoded thereby for CD4 . . . by at least two-fold." As such, Hasel does not disclose a second mutation "that detectably increases the level of the function or activity affected by the [V3 loop] deletion." Because Hasel does not disclose a second mutation that is a "compensatory mutation," it does not disclose each and every element of Applicants' presently claimed invention and, therefore, does not anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection of claim 1 under 35 U.S.C. § 102(b).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that the claims are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendments or additional claim. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

JAMES A. HOXIE, et al.

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Date

THOMAS M. SOSSONG, JR., Ph.D., J.D.
Registration No. 48,463
DRINKER BIDDLE & REATH LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Tel: (215) 988.2562
Fax: (215) 988.2757
Attorney for Applicants

dlp